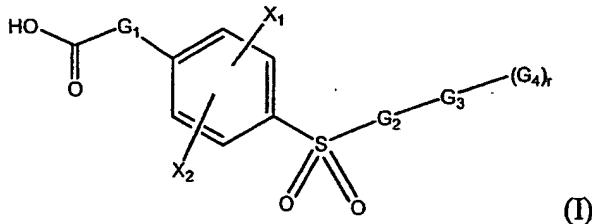


WE CLAIM:

1. A compound having the structure of Formula (I):



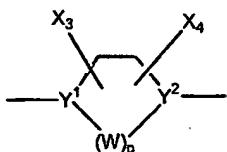
wherein:

5 G_1 is selected from the group consisting of $-(CR^1R^2)_n-$ and $-(CR^1R^2)_nO-$, wherein n is 1 or 2 and each R^1 and each R^2 are independently hydrogen,

10 C_{1-4} alkyl, C_{1-4} heteroalkyl, C_{1-4} alkoxy, and C_{1-4} perhaloalkyl or together may form a cycloalkyl, provided that R^1 and R^2 are not both H when n is 1;

X_1 and X_2 are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, cycloalkyl, halogen, perhaloalkyl, hydroxy, C_{1-4} alkoxy, nitro, cyano, and NH_2 ;

G_2 is a cyclic moiety having structure



15 wherein Y^1 and Y^2 are each independently N or $C-X_5$;

X_3 and X_4 are each independently selected from the group consisting of hydrogen, alkyl, halogen, C_{1-4} perhaloalkyl, hydroxy, alkoxy, nitro, cyano, NH_2 ;

20 p is 1, 2 or 3;

W is independently selected from the group consisting of $-CX_3X_4-$, $N-X_6$, and a moiety which together with Y^2 , forms a double bond;

X_5 is selected from the group consisting of hydrogen, alkyl, hydroxy, alkoxy, cyano, halogen, C_{1-4} perhaloalkyl and NH_2 ; provided further that

when X_5 is alkyl, alkoxy or C_{1-4} perhaloalkyl, then such groups may be optionally ligated to G_4 ;

X_6 is selected from the group consisting of hydrogen, alkyl, hydroxy, and

5 C_{1-4} perhaloalkyl, or null when forming a double bond with Y^2 ;

G_3 is selected from the group consisting of a bond, a double bond,

$-(CR^3R^4)_m-$, $-C(O)(CR^3R^4)_m-$, $-(CR^3R^4)_mC(O)-$, and $-$

$(CR^3R^4)_mCR^3=CR^4-$, wherein m is 0, 1, or 2, and wherein each R^3 and each R^4 is independently H, C_{1-4} alkyl, C_{1-4} alkoxy, aryl, C_{1-4} perhaloalkyl, cyano, and nitro; and

10 G_4 is selected from the group consisting of optionally substituted aryl, heteroaryl, cycloalkyl, cycloheteroaryl, and cycloalkenyl; and wherein

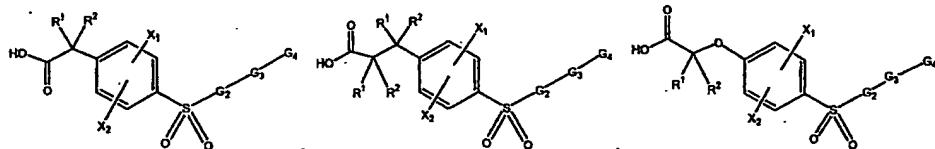
Y^2 is $C-X_5$, G_4 may be optionally ligated to X_5 ; and

15 r is 1 or 2;

or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof.

2. A compound according to claim 1 having a structural formula selected

20 from the group consisting of:

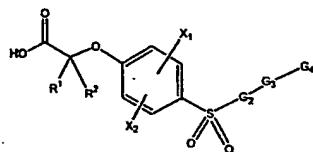


3. A compound according to claim 2, wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or

25 cyclohexyl..

4. A compound according to claim 3, wherein R^1 and R^2 are each methyl.

5. A compound according to claim 2 having the structure:



6. A compound according to claim 5, wherein R¹ and R² are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

5 7. A compound according to claim 6, wherein R¹ and R² are each methyl.

8. A compound according to claim 2, wherein X₁ and X₂ are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

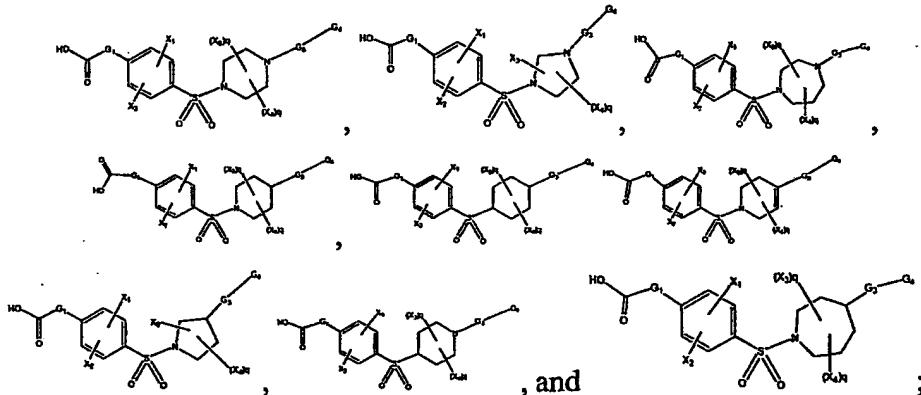
10 9. A compound according to claim 8, wherein X₁ and X₂ are each independently selected from the group consisting of hydrogen and methyl.

10 10. A compound according to claim 5, wherein X₁ and X₂ are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

15 11. A compound according to claim 10, wherein X₁ and X₂ are each independently selected from the group consisting of hydrogen and methyl.

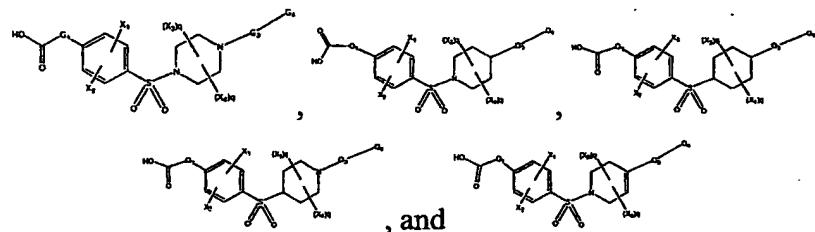
12. A compound according to claim 1 having a structural formula selected from the group consisting of:

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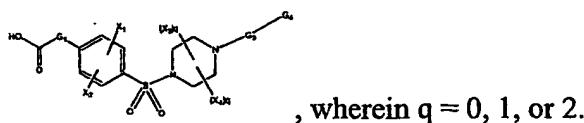


wherein $q = 0, 1, \text{ or } 2$.

13. A compound according to claim 12, wherein G_1 is selected from the group consisting of $-CR^1R^2-$, $-(CR^1R^2)_2-$, and $-CR^1R^2-O-$.
14. A compound according to claim 13, wherein G_1 is $-CR^1R^2-O-$.
15. A compound according to claim 14, wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
16. A compound according to claim 15, wherein R^1 and R^2 are each methyl.
17. A compound according to claim 12, wherein X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.
18. A compound according to claim 17, wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl, or together may form a cyclopropyl.
19. A compound according to claim 18, wherein R^1 and R^2 are each methyl.
20. A compound according to claim 12 having a structural formula selected from the group consisting of:



- 20 wherein $q = 0, 1$, or 2 .
21. A compound according to claim 20 having the structural formula:

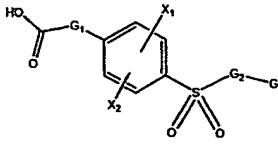
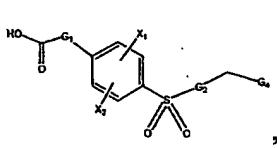
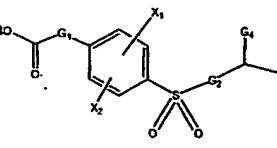


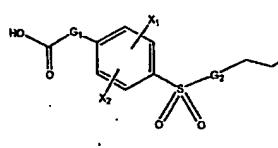
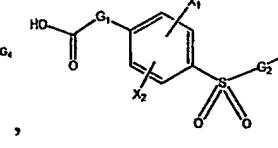
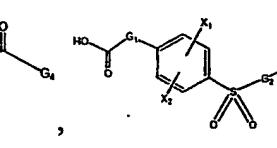
22. A compound according to claim 21, wherein G_1 is selected from the group consisting of $-CR^1R^2-$, $-(CR^1R^2)_2-$, and $-CR^1R^2-O-$.
23. A compound according to claim 22, wherein G_1 is $-CR^1R^2-O-$.
24. A compound according to claim 23, wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

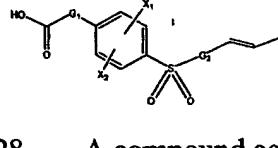
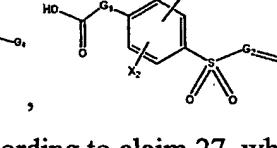
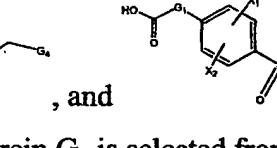
25. A compound according to claim 24, wherein R^1 and R^2 are each methyl.

26. A compound according to claim 21, wherein X_1 and X_2 are each independently selected from the group consisting of hydrogen, halogen, methyl, ethyl, and propyl.

5 27. A compound according to claim 1 having a structural formula selected from the group consisting of:


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, and

10 28. A compound according to claim 27, wherein G_1 is selected from the group consisting of $-CR^1R^2-$, $-(CR^1R^2)_2-$, and $-CR^1R^2-O-$.

29. A compound according to claim 28, wherein G_1 is $-CR^1R^2-O-$.

30. A compound according to claim 28, wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

15 31. A compound according to claim 30, wherein R^1 and R^2 are each methyl.

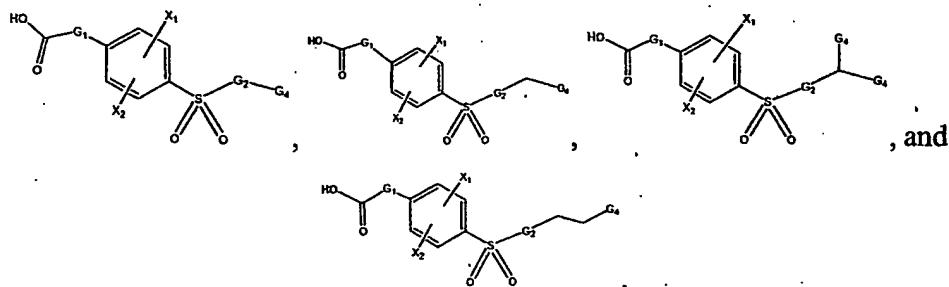
32. A compound according to claim 27, wherein X_1 and X_2 are each independently selected from the group consisting of hydrogen, halogen, methyl, ethyl, and propyl.

20 33. A compound according to claim 32, wherein G_1 is $-CR^1R^2-O-$.

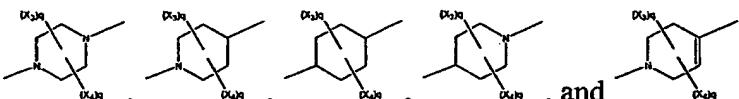
34. A compound according to claim 33, wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

25 35. A compound according to claim 34, wherein R^1 and R^2 are each methyl.

36. A compound according to claim 27 having a structural formula selected from the group consisting of:



37. A compound according to claim 36, wherein G₂ is selected from the group consisting of:



5

38. A compound according to claim 37, wherein G₁ is selected from the group consisting of -CR¹R²-, -(CR¹R²)₂-, and -CR¹R²-O-.

39. A compound according to claim 38, wherein G₁ is -CR¹R²-O-.

40. A compound according to claim 38, wherein R¹ and R² are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

41. A compound according to claim 40, wherein R¹ and R² are each methyl.

42. A compound according to claim 37, wherein X₁ and X₂ are each independently selected from the group consisting of hydrogen, halogen, methyl, ethyl, halogen, and propyl.

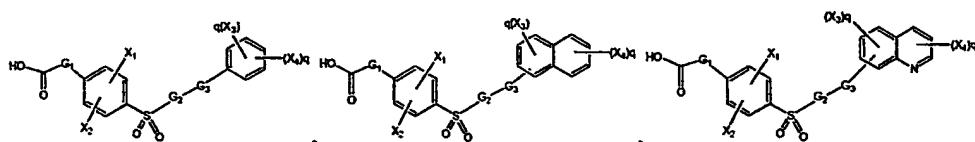
43. A compound according to claim 42, wherein G₁ is -CR¹R²-O-.

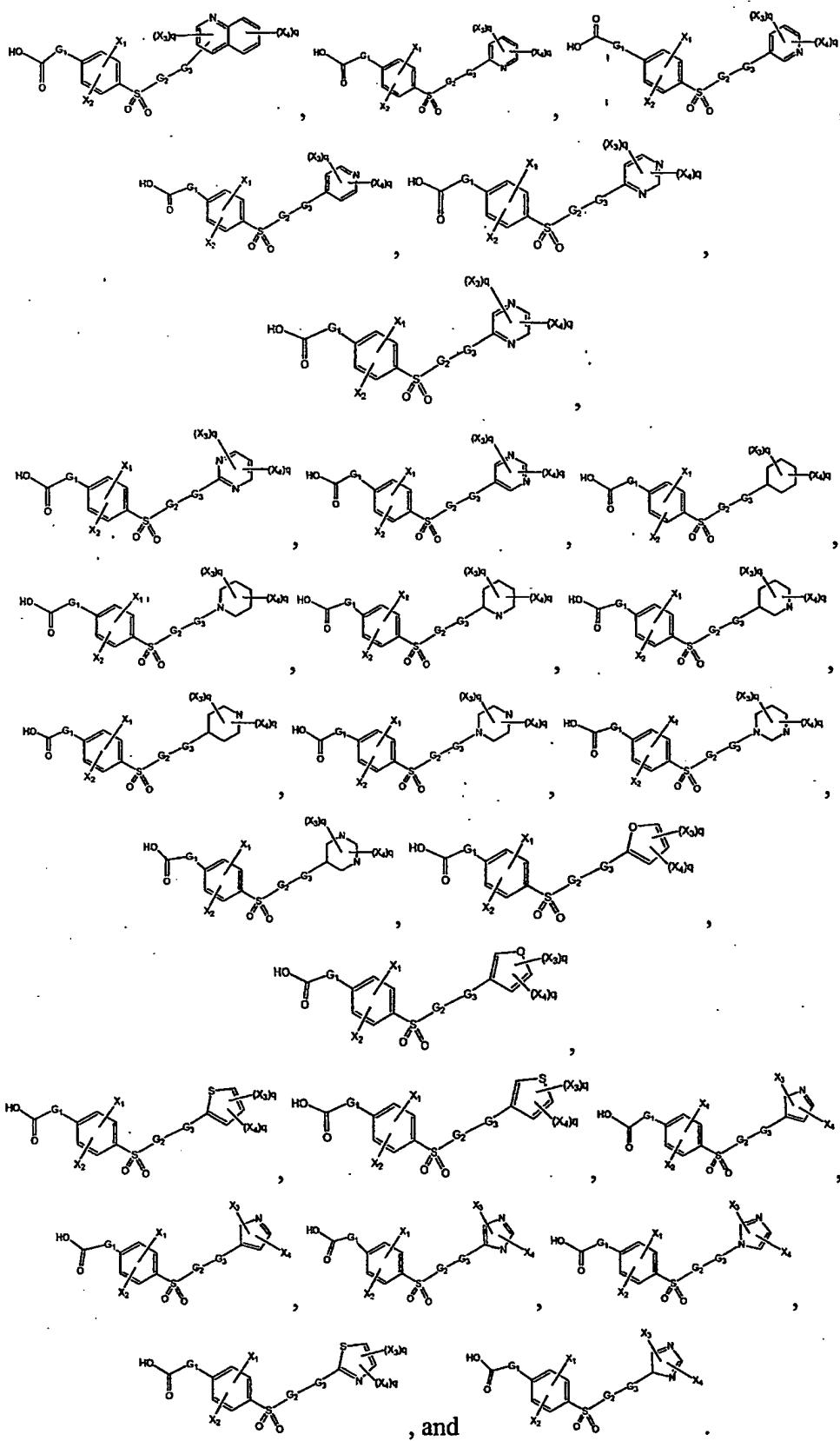
44. A compound according to claim 43, wherein R¹ and R² are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

45. A compound according to claim 44, wherein R¹ and R² are each methyl.

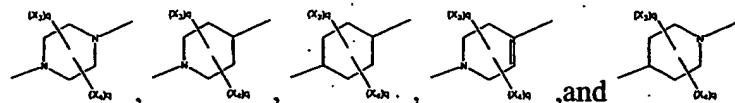
46. A compound according to claim 1 having a structural formula selected from the group consisting of:

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47. A compound according to claim 46, wherein G_2 is selected from the group consisting of:



48. A compound according to claim 47, wherein G_1 is selected from the group consisting of $-\text{CR}^1\text{R}^2-$, $-(\text{CR}^1\text{R}^2)_2-$, and $-\text{CR}^1\text{R}^2-\text{O}-$.

49. A compound according to claim 48, wherein G_1 is $-\text{CR}^1\text{R}^2-\text{O}-$.

50. A compound according to claim 48, wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

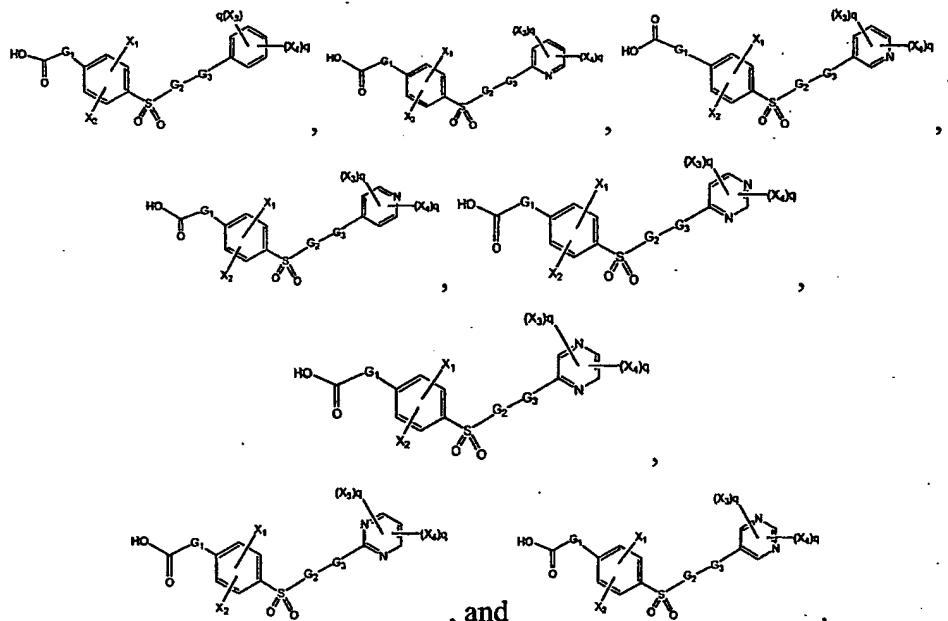
51. A compound according to claim 50, wherein R^1 and R^2 are each methyl.

52. A compound according to claim 47, wherein X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

53. A compound according to claim 46, wherein G_3 is either a bond or $-\text{CH}_2-$.

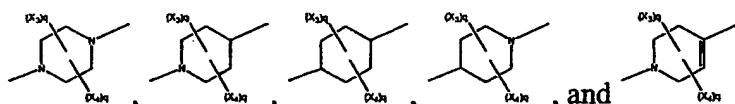
54. A compound according to claim 46 having a structural formula selected from the group consisting of:

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55. A compound according to claim 54, wherein G_2 is selected from the group consisting of:



56. A compound according to claim 54, wherein G_1 is selected from the group consisting of $-\text{CR}^1\text{R}^2-$, $-(\text{CR}^1\text{R}^2)_2-$, and $-\text{CR}^1\text{R}^2-\text{O}-$.

57. A compound according to claim 56, wherein G_1 is $-CR^1R^2-O-$.

58. A compound according to claim 56, wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

5 59. A compound according to claim 58, wherein R^1 and R^2 are each methyl.

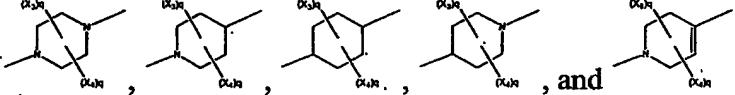
60. A compound according to claim 54, wherein X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

61. A compound according to claim 54, wherein G_3 is either a bond or $-CH_2-$.

10 62. A compound according to claim 54, wherein X_3 is selected from the group consisting of halogen and C_1-C_4 perhaloalkyl; and q is 1 or 2.

63. A compound according to claim 62, wherein X_3 is selected from the group consisting of F, Cl and CF_3 .

15 64. A compound according to claim 62, wherein G_2 is selected from the group consisting of:



65. A compound according to claim 62, wherein G_1 is selected from the group consisting of $-CR^1R^2-$, $-(CR^1R^2)_2-$, and $-CR^1R^2-O-$.

66. A compound according to claim 65, wherein G_1 is $-CR^1R^2-O-$.

20 67. A compound according to claim 65, wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

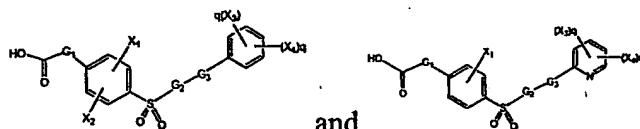
68. A compound according to claim 65, wherein R^1 and R^2 are each methyl.

69. A compound according to claim 62, wherein X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

25 70. A compound according to claim 62, wherein G_3 is either a bond or $-CH_2-$.

71. A compound according to claim 54 having a structural formula selected from the group consisting of:

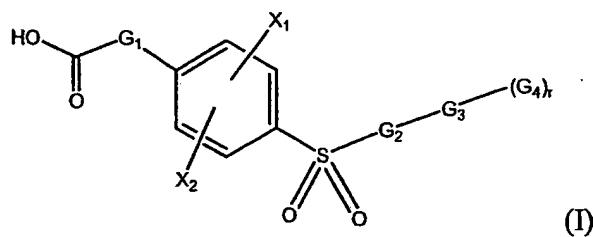
30



72. A compound according to claim 71, wherein X_3 is selected from the group consisting of halogen and C_1 - C_4 perhaloalkyl; and q is 1 or 2.

73. A compound according to claim 72, wherein X_3 is selected from the group consisting of F, Cl and CF_3 .

5 74. A compound having the structure of Formula (I)

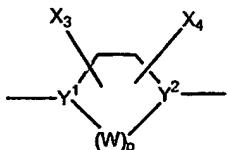


wherein:

G_1 is selected from the group consisting of $-(CR^1R^2)_n-$ and $-(CR^1R^2)_nO-$, wherein n is 1 or 2 and each R^1 and each R^2 are hydrogen;

10 X_1 and X_2 are each independently selected from the group consisting of hydrogen, C_1 - C_4 alkyl, cycloalkyl, halogen, perhaloalkyl, hydroxy, C_1 - C_4 alkoxy, nitro, cyano, and NH_2 ;

G_2 is a cyclic moiety having structure



15 wherein Y^1 and Y^2 are each independently N or $C-X_5$;

X_3 and X_4 are each independently selected from the group consisting of hydrogen, alkyl, halogen, C_1 - C_4 perhaloalkyl, hydroxy, alkoxy, nitro, cyano, NH_2 ;

p is 1, 2 or 3;

W is independently selected from the group consisting of $-CX_3X_4-$, $N-X_6$, and

20 a moiety which together with Y^2 , forms a double bond;

X_5 is selected from the group consisting of hydrogen, alkyl, hydroxy, alkoxy, cyano, halogen, C_1 - C_4 perhaloalkyl and NH_2 ; provided further that when X_5 is alkyl, alkoxy or C_1 - C_4 perhaloalkyl, then such groups may be optionally ligated to G_4 ;

25 X_6 is selected from the group consisting of hydrogen, alkyl, hydroxy, and

C_{1-4} perhaloalkyl, or null when forming a double bond with Y^2 ;

G_3 is selected from the group consisting of a bond, a double bond,

$-(CR^3R^4)_m-$, carbonyl, and $-(CR^3R^4)_mCR^3=CR^4-$, wherein m is 0, 1, or 2, and

wherein each R^3 and each R^4 is independently H, C_{1-4} alkyl, C_{1-4} alkoxy, aryl, C_{1-4}

5 C_{1-4} perhaloalkyl, cyano, and nitro; and

G_4 is selected from the group consisting of optionally substituted aryl,

heteroaryl, cycloalkyl, cycloheteroaryl, cycloalkenyl, wherein said optional

substituents are selected from the group consisting of alkyl, halogen,

perhaloalkyl, perhaloalkoxy, C_1-C_4 alkoxy; and wherein Y^2 is $C-X_5$, G_4 may be

10 optionally ligated to X_5 ; and

r is 1 or 2;

or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug,

pharmaceutically active metabolite, pharmaceutically acceptable salt,

pharmaceutically acceptable ester, pharmaceutically acceptable amide, or

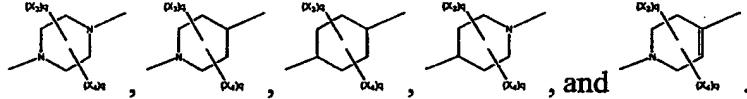
15 pharmaceutically acceptable solvate thereof.

75. A compound according to claim 74, wherein X_1 and X_2 are each

independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

76. A compound according to claim 74, wherein G_2 is selected from the group

20 consisting of:



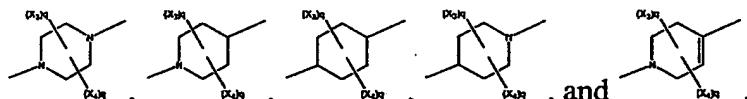
77. A compound according to claim 76, wherein G_1 is $-CR^1R^2-O-$.

78. A compound according to claim 77, wherein X_1 and X_2 are each

independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

25 79. A compound according to claim 74, wherein G_3 is either a bond or $-CH_2-$.

80. A compound according to claim 79, wherein G_2 is selected from the group consisting of:

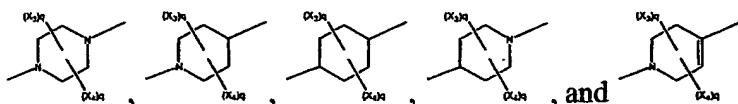


30 81. A compound according to claim 80, wherein G_1 is $-CR^1R^2-$.

82. A compound according to claim 79, wherein X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

83. A compound according to claim 74, wherein G_4 is selected from the group consisting of an optionally substituted phenyl, pyridyl, and pyrimidyl.

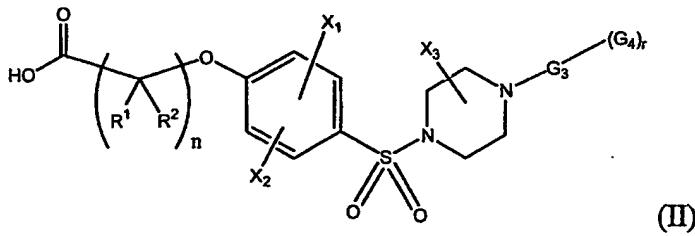
5 84. A compound according to claim 83, wherein G_2 is selected from the group consisting of:



10 85. A compound according to claim 84, wherein G_1 is $-CR^1R^2-$.

86. A compound according to claim 83, wherein X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

87. A compound having the structure of Formula (II)



wherein:

n is 1, 2, or 3;

each R^1 and each R^2 are independently hydrogen, C_{1-4} alkyl, C_{1-4} heteroalkyl, C_{1-4} alkoxy, and C_{1-4} perhaloalkyl or together may form a cycloalkyl, provided that R^1 and R^2 are not both H when n is 20 1;

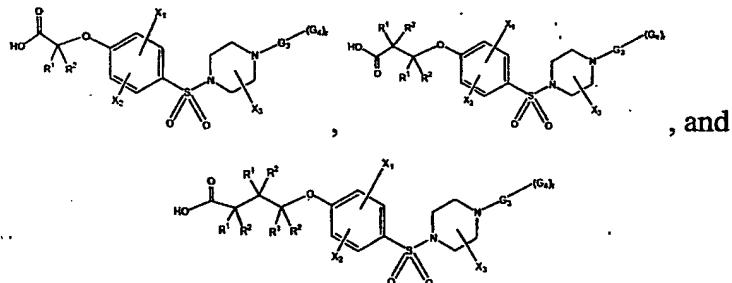
X_1 , X_2 , and X_3 are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, cycloalkyl, halogen, perhaloalkyl, hydroxy, C_{1-4} alkoxy, nitro, cyano, and NH_2 ;

25 G_3 is selected from the group consisting of a bond, $-(CH_2)_m-$, carbonyl, and $-(CH_2)CH=CH-$, wherein m is 1 or 2; and

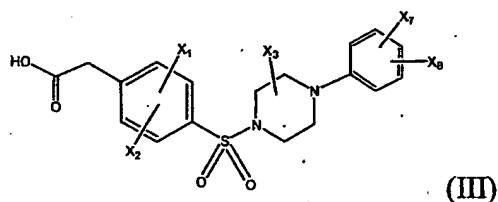
G_4 is selected from the group consisting of optionally substituted aryl, heteroaryl, cycloalkyl, and where r is 1 or 2; or a pharmaceutically acceptable salt, prodrug, or solvate thereof.

88. A compound according to claim 87 wherein said X_1 and X_3 is hydrogen or methyl.

5 89. A compound according to claim 88 having a structure selected from the group consisting of



10 90. A compound having the structure of Formula (III)



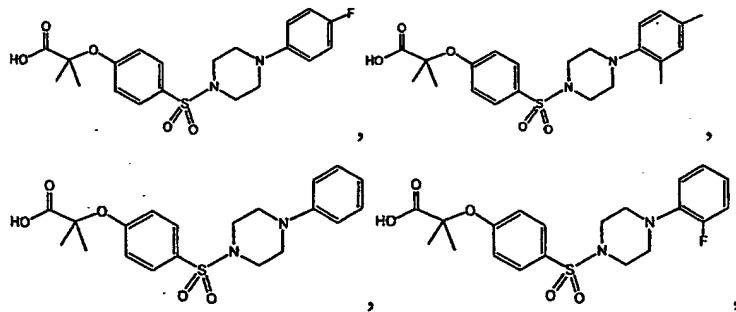
wherein:

X^1 , X^2 , and X^3 are each independently hydrogen or C_{1-4} alkyl;

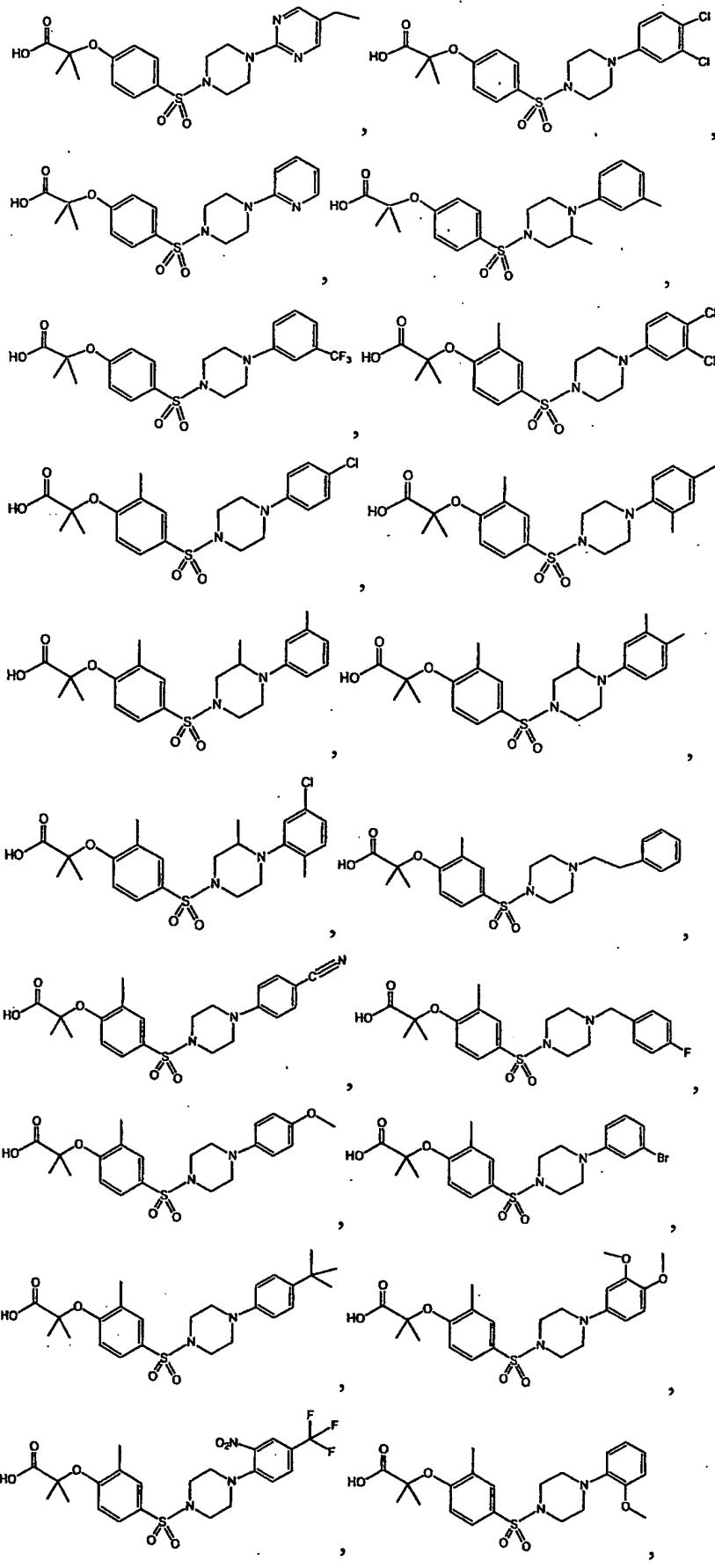
X^7 and X^8 are each independently selected from the group consisting of hydrogen,

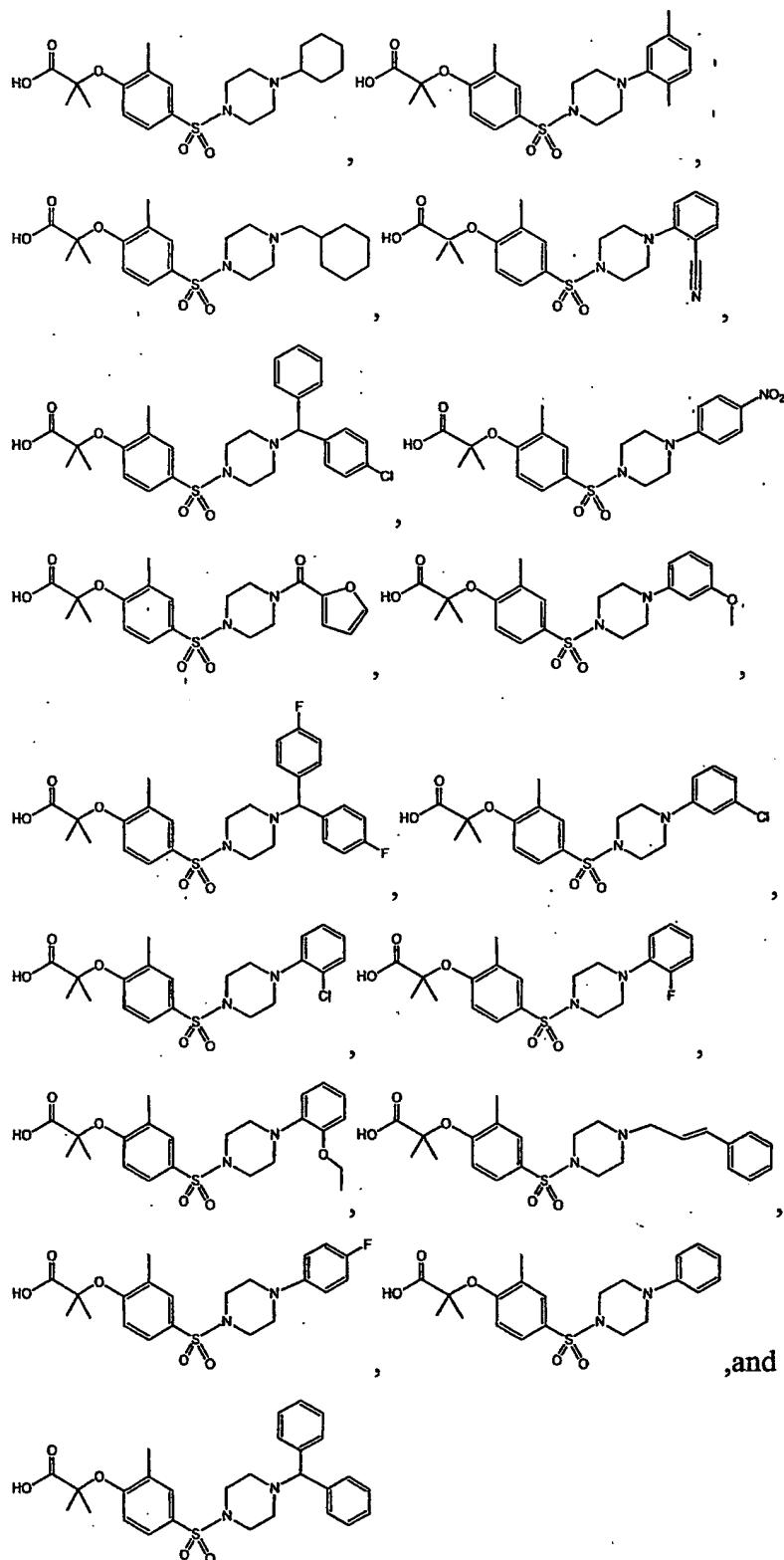
15 alkyl, halogen, C_{1-4} perhaloalkyl, hydroxy, alkoxy, nitro, cyano, and NH_2 ; or a pharmaceutically acceptable salt, prodrug, or solvate thereof.

91. A compound according to claim 1 having a structural formula selected from the group consisting of:



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92. A compound according to claims 1-91 which is an hPPAR-delta modulator.

93. A compound according to claim 92 which is a selective hPPAR-delta modulator.
94. A pharmaceutical composition comprising a compound of claims 1-93.
95. A pharmaceutical composition according to claim 94 further comprising a pharmaceutical acceptable diluent or carrier.
96. A compound or composition according to claims 92-95 for use in the treatment of a disease or condition ameliorated by the modulation of a hPPAR-delta.
97. A compound or composition according to claim 96 wherein said hPPAR-delta modulated disease or condition is dyslipidemia, metabolic syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type II diabetes mellitus, type 1 diabetes, insulin resistance hyperlipidemia, obesity, anorexia bulimia, inflammation and anorexia nervosa.
98. A compound or composition according to claims 92-95 for use in the manufacture of a medicament for the prevention or treatment of a disease or condition ameliorated by the modulation of a hPPAR-delta.
99. A compound, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt comprising a compound according to claims 1-91 having an EC₅₀ value less than 1 μM as measured by a functional cell assay.
100. A method for raising HDL in a subject comprising the administration of a therapeutic amount of a hPPAR-delta modulator compound according to claims 92-93.
101. Use of a hPPAR-delta modulator compound according to claims 92-93 for the manufacture of a medicament for the raising of HDL in a patient in need thereof.
102. A method for treating Type 2 diabetes, decreasing insulin resistance or lowering blood pressure in a subject comprising the administration of a therapeutic amount of a hPPAR-delta modulator compound according to claims 92-93.
103. Use of a hPPAR-delta modulator compound according to claims 92-93 for the manufacture of a medicament for the treatment of Type 2

diabetes, decreasing insulin resistance or lowering blood pressure in a patient in need thereof.

104. A method for decreasing LDLc in a subject comprising the administration of a therapeutic amount of a hPPAR delta modulator compound according to claims 92-93.

5 105. Use of a hPPAR-delta modulator compound according to claims 92-93 for the manufacture of a medicament for decreasing LDLc in a patient in need thereof.

106. A method for shifting LDL particle size from small dense to normal dense LDL in a subject comprising the administration of a therapeutic amount of a hPPAR-delta modulator compound according to claims 92-93.

10 107. Use of a hPPAR-delta modulator compound according to claims 92-93 for the manufacture of a medicament for shifting LDL particle size from small dense to normal LDL in a patient in need thereof.

15 108. A method for treating atherosclerotic diseases including vascular disease, coronary heart disease, cerebrovascular disease and peripheral vessel disease in a subject comprising the administration of a therapeutic amount of a hPPAR-delta modulator compound according to claims 92-93.

20 109. Use of a hPPAR-delta modulator compound according to claims 92-93 for the manufacture of a medicament for the treatment of atherosclerotic diseases including vascular disease, coronary heart disease, cerebrovascular disease and peripheral vessel disease in a patient in need thereof.

25 110. A method for treating inflammatory diseases, including rheumatoid arthritis, asthma, osteoarthritis and autoimmune disease in a subject comprising the administration of a therapeutic amount of a hPPAR-delta modulator compound according to claims 92-93.

30 111. Use of a hPPAR-delta modulator compound according to claims 92-93 for the manufacture of a medicament for the treatment of inflammatory diseases, including rheumatoid arthritis, asthma, osteoarthritis and autoimmune disease in a patient in need thereof.

112. A method of treatment of a hPPAR-delta mediated disease or condition comprising administering a therapeutically effective amount of a compound according to any of claims 1-91 or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.
- 5 113. A method of modulating a peroxisome proliferator-activated receptor (PPAR) function comprising contacting said PPAR with a compound of Claims 1-91 and monitoring a change in cell phenotype, cell proliferation, activity of said PPAR, or binding of said PPAR with a natural binding partner.
- 10 114. The method of Claim 113, wherein said PPAR is selected from the group consisting of PPAR-alpha, PPAR-delta, and PPAR-gamma.
115. A method of treating a disease comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claims 1-91 to said patient wherein said disease is selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury.
- 20 116. A compound according to claims 1-91 which modulates a peroxisome proliferator-activated receptor (PPAR) function.
117. A compound of Claim 116, wherein said PPAR is selected from the group consisting of PPAR α , PPAR δ , and PPAR γ .
- 25 118. A compound or composition according to claim 116 for use in the treatment of a disease or condition ameliorated by the modulation of a PPAR.
119. A compound or composition according to claim 118 wherein said disease or condition is dyslipidemia, metabolic syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type II diabetes mellitus, type 1 diabetes, insulin resistance hyperlipidemia, obesity, anorexia bulimia, inflammation and anorexia nervosa.

120. The compound or composition of Claim 118, wherein said PPAR is selected from the group consisting of PPAR α , PPAR δ , and PPAR γ .
121. A compound or composition according to claims 116 for use in the manufacture of a medicament for the prevention or treatment of disease or condition ameliorated by the modulation of a PPAR.
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122. The compound or composition of Claim 121, wherein said PPAR is selected from the group consisting of PPAR α , PPAR δ , and PPAR γ .